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Formulation Development of Aqueous Topical Solutions and Gels of Poorly Water Soluble Drug Nimesulide, Using Novel Application of Mixed Solvency Concept and their Evaluations

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Abstract: ***Aim: Application of mixed solvency concept has been employed in the present research work to develop the topical solutions and gels of poorly water soluble drug, nimesulide. Materials and Methods: For poorly water soluble drug nimesulide, combination of solubilizers such as sodium benzoate, sodium caprylate , sodium oleate, propylene glycol and benzyl alcohol as mixed solvent systems were used to decrease the overall concentration of solubilizers required to produce substantial increase in solubility of drug and thereby resulting in expected enhanced permeation of nimesulide from its topical formulations. The procured sample of nimesulide was characterized by melting point, IR, UV and DSC studies. The formulations were evaluated for various properties of solution such as pH, viscosity, freeze thaw study and thin layer chromatography. Stability studies of topical solutions and gels were performed for three months at room temperature and 2 to 8 ˚C. Results and Discussion: It was found that 91.5% at room temperature and 91.4% at 2 to 8º C of drug was remaining after stability study for three months at respective temperatures in batch first and 91.8 %, at room temperature, 91.6% at 2 to 8º C in batch second. The percent drug remaining of first formulation of gel at room temperature was 92.7% and at 2 to 8º C it was 92.3 % after three months. Conclusion: Mixed solvency concept was successfully employed to improve the solubility and permeation of poorly water soluble drug, nimesulide***

Keywords: Solubility, nimesulide, topical solution, topical gel, mixed solvency concept, NSAID

1. Introduction

Drug delivery through topical route represents a most convenient and novel approach for the application to the skin for direct treatment of cutaneous disorder or the cutaneous manifestation of a general disease having the intent of containing the pharmacological or different other effects of the drug for the surface of the skin and within the skin.

One of the oldest dosage form which is used in the treatment of disease and has the rapid and very high absorption of soluble medicinal products is solution. The solution which is applied directly to skin is called topical solution[1]. Two major key characteristics that need to be taken under the consideration while compounding the solutions are solubility and stability. Topical solution acts locally and targets at the site of allergy and inflammation resulting in reduced side effects and toxicity to other organs. Low aqueous solubility is the main problem for the formulation development of the various other new chemical entities as well as for various generic developments. Water is the main solvent chosen for liquid pharmaceutical formulations. Solubility improvement techniques include derivatization, surfactant solubilisation , alteration of pH, cosolvency, hydrotropic solubilisation, mixed solvency concept.

As per the mixed solvency concept proposed by Maheshwari[2-5], each and every substance present in the universe has got solubilizing property i.e. all the liquids, gases and solids possess solubilizing power. As per his statement each substance is solubilizer. A concentrated aqueous solution containing various water soluble substances may act as good solvent for poorly water soluble drugs. Such concentrated solutions may show synergistic or additive solubilizing actions of solubilizers present in the solution. Each and every weaker solvent (for a solute) can be made a strong solvent by proper selection of solubilizers. The concept of mixed solvency has been used to show the enhancement of aqueous solubility of a large number of poorly water soluble drugs by employing the mixed solvency concept.[6-30]

Application of mixed solvency has been employed in present research work to develop the topical solutions of nimesulide (used as model poorly water soluble drug). It is white to pale yellow crystalline powder, practically insoluble in water. It is soluble in ethanol, ether, acetone and castor oil (Figure 1). Mixed-solvency can be employed as a tool to decrease the overall concentration of solubilizers required to produce substantial increase in solubility and thereby resulting in enhanced permeation of nimesulide in its topical dosage form.

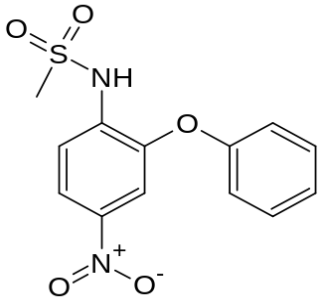

Figure 1: Structure of Nimesulide

2. Materials and Methods

2.1 Materials

Nimesulide drug sample was a generous gift by Schon Pharmaceuticals Limited. (Indore). All other chemicals used were of analytical grade and procured from local market. A Shimadzu-1700 UV-Visible spectrophotometer with 1 cm matched silica cells were used for spectrophotometric analysis.

2.2 Estimation of nimesulide

2.2.1 UV spectrophotometric analysis of nimesulide:

20 µg/ml solution of drug was scanned in demineralised water on a double-beam UV-visible spectrophotometer (Shimadzu® 1700) between wavelength ranges of 200 nm to 400 nm. U.V spectrum was recorded in figure 2.

2.2.2 IR analysis of drug sample:

The infrared spectroscopy of nimesulide was performed for identification of drug. About 1-5 mg of the sample was triturated with approximately 300 mg of dry, finely powdered potassium bromide IR and compressed as pellet and spectra was recorded on FTIR spectrophotometer (Shimadzu 8400S). The IR spectrum is presented in figure 3.

2.2.3 DSC analysis of drug sample:

In order to obtain the DSC thermograms of the drug, a thermal analysis instrument, TA Instruments-2910 modulated DSC (USA) was employed. To carry out these studies, 1-4 mg of drug was weighed accurately and placed in one of the matched aluminum pan. The sample pan and the reference pan both were sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of 10˚C/min with a continuous purge of nitrogen (45 CC/min) was done with recording of energy changes in the sample with respect to the reference in the temperature range of 80-200˚C. The DSC thermogram is shown in the figure 4.

2.2.4 Preparation of calibration curve of nimesulide in Milli –Q water:

Fifty mg of nimesulide was accurately weighed and transferred to a 50 ml volumetric flask. To this, 20 ml of 30% blend (10% sodium benzoate, 10% sodium caprylate, 10% sodium oleate solution) was added to dissolve the drug and the volume was made up to 50 ml with Milli-Q water to get stock solution of 1000µg/ml. Then, 1ml solution was taken in a 50ml volumetric flask and it was diluted with Milli-Q water upto 50 ml. The concentration of this resulting solution was 20 µg/ ml. Appropriate dilutions were made from stock solution with Milli-Q water to give concentration range of 10, 20, 30 and 40 µg/ml. The absorbances of the resulting drug solutions were observed using a double beam UV/Visible spectrophotometer (Shimadzu 1700) at 391 nm against the respective reagent blanks.

2.3 Determination of interference of excipients in the spectrophotometric estimation of nimesulide:

Different excipients: sodium benzoate, sodium caprylate, sodium oleate, propylene glycol and benzyl alcohol were used for the interference study. For determination of interference of excipients in the spectrophotometric estimation of nimesulide, the absorbances of the standard solutions of nimesulide were determined in Mili Q water alone and in the presence of the excipients. The absorbances were recorded against respective reagent blanks at 391 nm. Results are shown in table 6 .

2.4 Drug solubilizers incompatibility studies

The different formulation components involved in the development of proposed formulations were physically mixed with drug in 1:1 ratio and filled in glass vials properly capped and sealed. The vials of each sample were kept at room temperature and in refrigerator and for one month period. After every week for one month, the vials were withdrawn and changes in physical appearance (if any) and color of the contents were observed.

2.5 Solubility studies

Solubility of nimesulide in distilled water and in different solvent systems were determined by equilibrium solubility method. The excess drug was added to 5 ml of distilled water and mixed solvent systems contained in 10 ml glass vials and vials were sealed with rubber closures and aluminium seals. The vials were shaken for 12 hr in Orbital Flask Shaker (Khera Instrument Pvt. Ltd., Delhi, India) and then allowed to equilibrate for 24 hrs undisturbed. The solutions containing excess of drug were centrifuged at 2200 r.p.m. for 5 minutes in ultra-centrifuge and filtered through Whatman grade 5 filters. Aliquots of the filtrate were suitably diluted with distilled water and the dilutions were analyzed on UV-Visible spectrophotometer (Shimadzu 1700) against respective reagent blanks. Results are shown in table.1

Table 1: Solubility data of Nimesulide in different solvent systems

S. No	Solvent systems	Solubility (mg/ml)	Inference
1.	Water	0.017	Practically insoluble
2.	Phosphate buffer (pH 7.4)	0.053	Practically insoluble
3.	10% Polyethylene glycol 400	0.348	Very slightly soluble
4.	Benzyl alcohol	4.12	Slightly soluble
5.	PEG 400	42.67	Soluble

2.6 Formulation development of topical solution

Solubility determination of Nimesulide in various aqueous solutions of solubilizers (blends). In order to make 10ml of blend A, 1gm sodium benzoate and 1gm sodium caprylate were taken in a 10ml volumetric flask. About 7ml of Milli-Q water was added and flask was shaken for about 10-15 min on vortex shaker. After complete dissolution of solubilizers, volume was made up to 10ml with Milli-Q water. Same procedure was followed for preparing other blends.

For determination of approximate solubility, one ml of above solution was taken in a 10 ml volumetric flask and 5mg nimesulide drug was added in the flask .The flask was shaken for 5 to 10 minutes, if the drug was dissolved then 5 mg drug was added. The drug was added until the solution

gets turbid. The approximate solubilities of drug were reported in table -2

Table 2: Results of approximate solubility studies of Nimesulide in various aqueous solutions of solubilisers

Blend	Composition of blends (w/v)	Solubility (mg/ml)
A	10% w/v sodium benzoate 10% w/v sodium Capryalte	5
B	10% w/v sodium benzoate 10% w/v sodium oleate	10
C	10% w/v sodium benzoate 10% w/v sodium caprylate 10% w/v sodium oleate	20
D	10% w/v sodium benzoate 10% w/v sodium oleate 10% w/v sodium caprylate 10% v/v propylene glycol	30
E	10% w/v sodium benzoate 10% w/v sodium caprylate 10% w/v sodium oleate 10% v/v benzyl alcohol	45
F	5% w/v sodium benzoate 10% w/v sodium oleate 10% w/v sodium caprylate 5% v/v benzyl alcohol 10% v/v propylene glycol	50
G	10% w/v sodium benzoate 10% w/v sodium caprylate 10% w/v sodium oleate 5% v/v benzyl alcohol 10% v/v propylene glycol	45
H	10% w/v sodium benzoate 10% w/v sodium caprylate 10% w/v sodium oleate 2.5%v/v benzyl alcohol 10% v/v propylene glycol	55
I	10%w/v sodium benzoate 10%w/v sodium caprylate 2.5% w/v sodium oleate 7.5 %v/v benzyl alcohol 10%v/v propylene glycol	45
J	5% w/v sodium benzoate 5% w/v sodium caprylate 5% w/v sodium oleate 5% v/v benzyl alcohol 10% v/v propylene glycol	35
K	7.5% w/v sodium benzoate 2.5 % w/v sodium caprylate 2.5 % w/v sodium oleate 7.5 % v/v benzyl alcohol 10 % v/v propylene glycol	20
L	2.5% w/v sodium benzoate 7.5% w/v sodium caprylate 7.5% w/v sodium oleate 2.5% v/v benzyl alcohol 10% v/v propylene glycol	20

Results

Significant increase in solubility of nimesulide was observed in Blend –J and Blend –K. So, these blends were selected for further studies on the basis of percentage of topical gel and solution of drug nimesulide

Preparation of Blend-J (Nimesu-J-F) (Table-3) - 2.5g sodium benzoate, 2.5 g sodium caprylate, 2.5 g sodium oleate, 2.5ml benzyl alcohol, 5ml propylene glycol were taken in a 50 ml volumetric flask. Then, 30 ml Mili-Q water was added and flask was shaken to dissolve the contents. Then remaining amount of water was added to make up the volume. Then it was transferred to air tight container. Fifteen ml of blend J was added in 25 ml volumetric flask and the drug nimesulide 0.5 g was added. Then, it was dissolved and the volume was made upto 25 ml with blend-J. Then, it was transferred to air tight container. Similarly, Nimesu-K-F (Table-4) was prepared.

Table 3: Formulation composition of Nimesu-J-F batch (for 25ml batch)

Composition	Quantity (for 100 ml)	Quantity (for 25 ml)
Drug (Nimesulide)	2 gms	0.5gm
Sodium benzoate	5 gms	2.5gm
Sodium caprylate	5 gms	2.5gm
Sodium oleate	5 gms	2.5gm
Benzyl alcohol	5 ml	2.5ml
Propylene glycol	5 ml	5 ml
Milli-Q water	q.s.100 ml	q.s. 25 ml

Table 4: Formulation composition of Nimesu-K-F batch (for 25ml batch)

S.No.	Name of ingredients	Quantity (for 100 ml)	Quantity (for 25ml)
1.	Drug (Nimesulide)	1 gm	0.25gm
2.	Sodium benzoate	7.5 gms	3.75gm
3.	Sodium oleate	2.5 gms	1.25gm
4.	Sodium caprylate	2.5 gms	1.25gm
5.	Benzyl alcohol	7.5 ml	3.75ml
6.	Propylene glycol	10 ml	5.0ml
7.	Milli-Q water	q.s. 100ml	q.s. 25 ml

2.7. Formulation development of aqueous topical gel

Preparation of Nimesu-K-G

2.5g sodium benzoate , 2.5 g sodium caprylate, 2.5 g sodium oleate , 2.5ml benzyl alcohol, 5ml propylene glycol were transferred in a 50 ml volumetric flask. Then, about 25ml of Milli-Q water was added and the flask was shaken to dissolve the contents. Accurately weighed 1.0 gm of drug nimesulide was transferred it into above solution and it was shaken upto 5 to 10 minutes to solubilise the drug. Then, sufficient Milli-Q water was added to make up the volume upto 50 ml.

In the other beaker 15ml Milli-Q water was taken and the polymer 1.0 gm Carbopol 974 was added gradually at 40-50^{o}C with continuous stirring on water bath avoiding the bubble formation. When the transparent gel was prepared, the above solution (about 25 ml) was added gradually into it with continuous stirring. The volume was made up to 50ml with Milli -Q water. Then, the prepared gel was cooled by

using ice bath and the consistency of gel was checked. Then the gel was stored in airtight container. The same procedure was followed for preparation of Nimesu-J-G topical gel formulation. The compositions used for both batches of gel formulations were recorded in Table 5

Table 5: Composition for different formulations of aqueous topical gels of Nimesulide

Batch code	Composition of gel (for 50ml)	Concentration of drug (%w/v)	Observation of gel formulation at RT after 72 hours
Nimesu-K-G	Drug (nimesulide) 0.5gm Sodium benzoate 3.75gms Sodium caprylate 1.25gms Sodium oleate 1.25gms Benzyl alcohol 3.75 ml Propylene glycol 5.0 ml Carbopol 974 P 1.0 gm Milli Q water up to 50ml	1.0	Clear , transparent gel
Nimesu-J-G	Drug (nimesulide) 1.0gm Sodium benzoate 2.5gm Sodium oleate 2.5gm Sodium caprylate 2.5gm Benzyl alcohol 2.5ml Propylene glycol 5.0ml Carbopol 974 P 1.0gm Milli Q water up to 50 ml	2.0	Clear , transparent gel

3. Results and discussion

3.1 Drug Characterization:

3.1.1 UV spectrophotometric analysis of nimesulide: The nimesulide drug sample exhibited a peak at 391 nm which was comparable to the value reported in the literature.

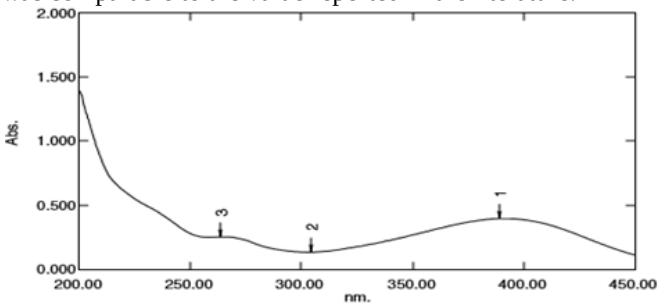

Figure 2: U. V. spectra of nimesulide in demineralized water

3.1.2. IR analysis of drug sample: The FTIR spectrum of drug sample had shown identical peaks as reported in reference sample of nimesulide.

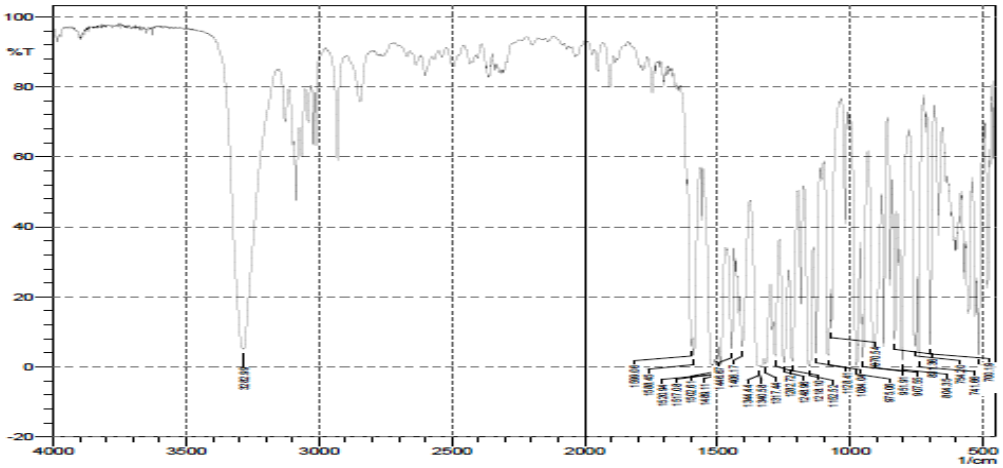

Figure 3: IR spectrum of nimesulide drug sample

3.1.3 DSC analysis of drug sample

The DSC curve of the crystalline form of nimesulide showed a sharp endothermic peak at 150.14˚C attributable to melting point.

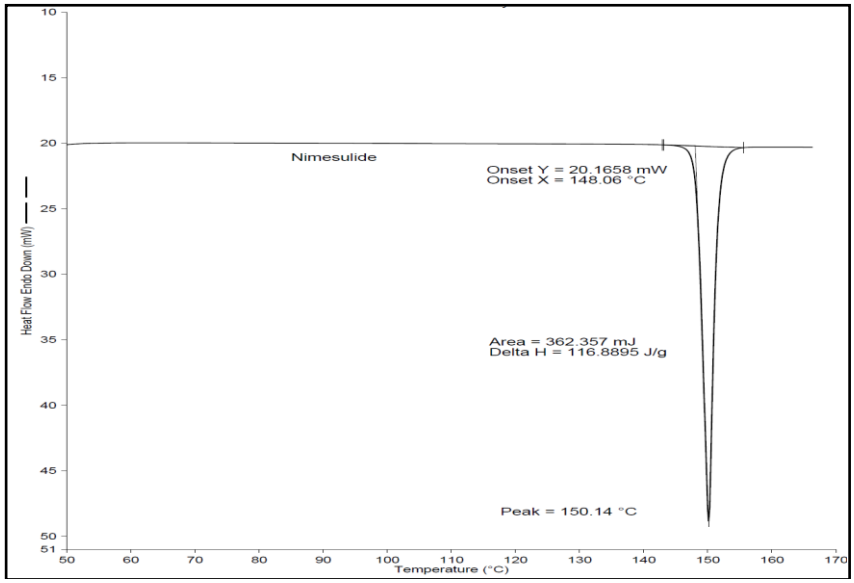

Figure 4: DSC thermogram of nimesulide drug sample

3.2 Preformulation studies

3.2.1 Preparation of calibration curve of nimesulide in Mili Q water

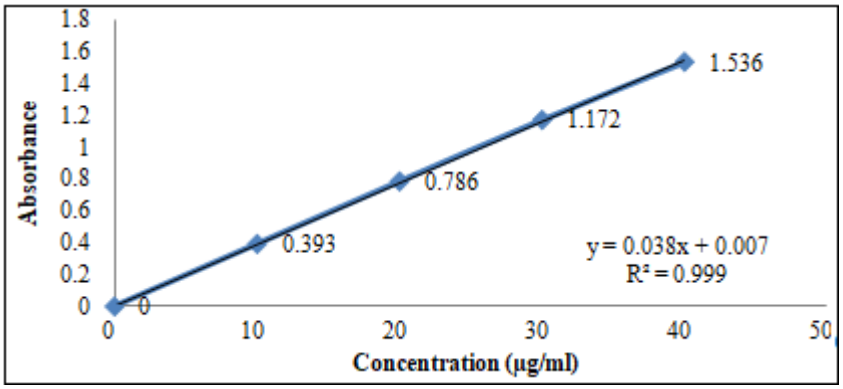

Figure 5: Calibration curve of nimesulide in Mili-Q water

3.2.2. Drug –solubilizers interference studies in the spectrophotometric estimation of Nimesulide

Table 6: Drug-solubilizers interference studies in the spectrophotometric estimation of Nimesulide

Drug	Solubilizer	Drug conc. (µg/ml)	Solubilizer conc. (µg/ml)	Wavelength (nm)	Absorbance against respective reagent blank
Nimesulide	-	20	-	391	0.782
Nimesulide	Sodium benzoate	20	200	391	0.784
Nimesulide	Sodium caprylate	20	200	391	0.786
Nimesulide	Sodium oleate	20	200	391	0.781
Nimesulide	Propylene glycol	20	200	391	0.787
Nimesulide	Benzyl alcohol	20	200	391	0.783
Nimesulide	Carbopol 974 P	20	200	391	0.789

3.3 Evaluations of solutions and gels

3.3.1 TLC analysis: From TLC study, in Table-7, it is clear that there is no significant change in R_f value indicating that there were no interactions between drug and solubilizers.

Table 7: TLC analysis of pure nimesulide and its formulations

S. No.	Mobile phase	R_f value		Inference
		Drug	1:3 TS	No significant change in R_f value, hence no interaction between drug and solubilizer
1	Toluene: Ethyl acetate (8:2)	0.71	0.69	
2.	Sodium benzoate (30% w/v)	0.68	0.66	No significant change in R_f value, hence no interaction between drug and solubilizer

3.3.2 pH of topical solutions of nimesulide: Take 5 ml of topical solution in a dry 25 ml beaker and the pH was recorded using Cyberscan 510 pH meter fitted with an electrode. Preferably the pH of topical solutions should be in the range of 6.8-7.0 . The pH of topical gel should be in the range of 4.3-4.5. Observations were recorded in Table 8

Table 8: pH data of final formulations of topical solutions and gels

S.No	Final Formulations	pH
1.	Nimesu-J-F	6.80
2.	Nimesu-K-F	6.90
3.	Nimesu-J-G	4.41
4.	Nimesu K-G	4.50
5.	Marketed Gel	4.51

3.3.3 Viscosity: The viscosity of aqueous topical solution was measured on LVS Brookfield Viscometer Model D attached T-bar spindle F. The required quantity of aqueous topical solution was placed in a beaker and spindle was lowered perpendicularly taking care that it doesn't touch the bottom of the beaker and also doesn't come out of the surface during study. The spindle was rotated in the gel at 3 rpm. By multiplying the dial reading with the factor corresponding to the spindle type and r.p.m. given in the brook-field viscometer catalogue the viscosity of the solutions and gels was obtained and recorded in the table 9 .

Table 9: Viscosity evaluation data of prepared aqueous topical gel formulations

S.No	Final Formulations	Viscosity (in cps)
1.	Nimesu- J-F	1890
2.	Nimesu-K-F	1740
3.	Nimesu-J-G	45210
4.	Nimesu-K-G	43296
5.	Marketed Gel	43125

3.3.4 Freeze Thaw testing: Two vials of each topical solution were subjected to freeze-thaw stress testing to observe any chance of precipitation. For 24 hr, the vials were stored at 2-8°C in refrigerator and then vials were kept at 40°C in oven for 24 h. Then the vials were placed at room temperature. After this, again, vials were kept at 2-8°C in refrigerator for 24 h. After 7-7 such alternate cycles at 2-8°C, room temperature, and 40°C the vials were observed for any precipitation or turbidity.

3.3.5. Stability studies: Stability studies of topical nimesulide solutions were performed for three months at room temperature and 2 to 8 º C. Percent drug remaining for formulation Nimesu J-F at room temperature was 91.5% and at 2 to 8˚C was 91.4%. Percent drug remaining for formulation Nimesu K-F at room temperature was 91.8%, at 2 to 8˚C was 91.6%. Percent drug remaining of formulation of gel Nimesu-K-G at room temperature was 92.8% and 2 to 8º C was 92.3%. The results of stability studies of nimesulide topical solutions and gels gave reasonably good results.

3.3.6. Drug content

To determine the drug content of solution, 1 ml topical solution was taken in 50 ml volumetric flask. Sufficient pH 7.4 buffer was added and the flask was shaken for 15 minutes and then, volume was made upto 50 ml with phosphate buffer pH 7.4.Then, it was diluted appropriately and was analyzed spectrophotometrically. The results were summarized in table 10.

To determine the drug content of gel, accurately weighed 1gm of gel was taken in a 50ml volumetric flask. Sufficient pH 7.4 buffer was added and the flask was sonicated for 15 minutes to solubilize the gel and then volume was made up to 50ml with pH 7.4 phosphate buffer. The solution so obtained was filtered using Whatman filter paper no.41. The filtrate was diluted appropriately and was analyzed spectophotometrically. The results are summarized in following table.10

Table 10: Drug content data of final batches of gel formulations

S No.	Topical formulations	Percent drug content
1.	Nimesu-J-F	1.940 % v/v
2.	Nimesu-K-F	0.948% v/v
3.	Nimesu-J-G	1.836% w/w
4.	Nimesu—K-G	0.981% w/w

3.3.7 In-Vitro drug release study of developed topical solution (batch Nimesu-K-F)

3.3.7.1 Experimental conditions:

- **Release Medium -** Phosphate buffer 7.4 pH
- **Volume of medium -** 200 ml
- **Temperature -** 37°C
- **Rotation -** 500 rpm

3.3.7.2. Procedure for In-vitro drug release study

The % drug release of the developed topical solution was done by filling 1 ml of the developed topical solution in the dialysis membrane placed in a 250 ml beaker containing 200 ml of phosphate buffer 7.4 pH. Ten ml of sample was removed after regular intervals and replaced with equal volume of phosphate buffer 7.4 pH to maintain the sink condition. The samples were analyzed using double beam UV-visible spectrophotometer (Shimadzu 1700) at 391 nm. The area of contact of gel/solution with the medium was 15 cm^2. Results were plotted in Fig.6

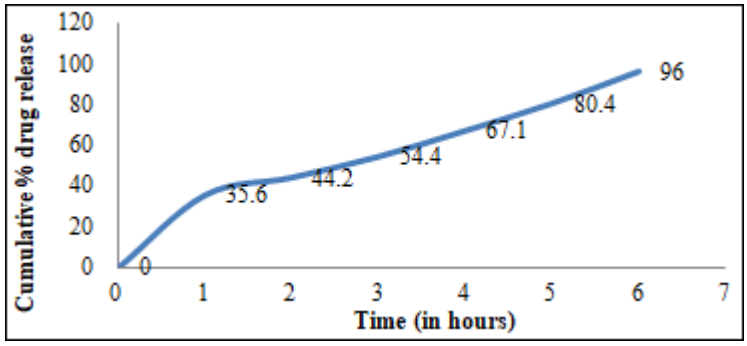

Figure 6: In-Vitro drug release study curve between cumulative % drug release and time for batch Nimesulide K-F

3.3.8. In-vitro drug release study of topical gel

Release studies was done using 1 g of formulated gel in the dialysis bag by placing it in a 250 ml beaker which contains 200 ml of phosphate buffer pH 7.4. Ten ml of sample was withdrawn at intervals of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12th hours. This was replaced with equal volume of buffer in order to maintain sink condition. The drug release data of formulated and marketed batches were recorded. Results were plotted in Fig. 7 and Fig. 8

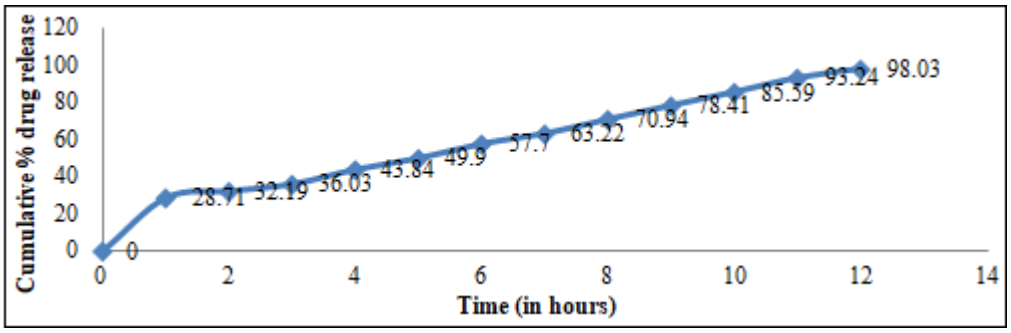

Figure 7: In-Vitro drug release study curve between cumulative % drug release and time for batch Nimesu-K-G

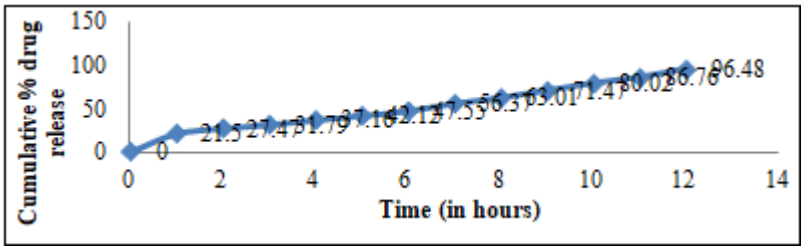

Figure 8: In –Vitro drug release study curve between cumulative % drug release and time for marketed formulation

3.4 In-vitro drug permeation study of aqueous topical gel formulation through goat ear skin

3.4.1. Permeation study

The drug permeation study of marketed products of nimesulide namely Nimesu gel of composition (1% nimesulide w/w) and aqueous topical gel of drug nimesulide (formulation code Nimesu-K-G) were carried out using a Franz diffusion cell with an effective surface area of 5.31 cm^2. The prepared goat ear skin was sandwiched between the receptor and donor compartments. Small magnetic stir bar was placed in the receptor compartment containing phosphate buffer having pH 7.4. The particulars of drug permeation study are given below:

Parameters	Description
Drug permeation medium	Phosphate buffer pH 7.4
Volume of diffusion cell	15.5 ml
Sampling volume	3 ml
Temperature of medium	32 ± 0.5^{o}C
Thickness of goat ear skin	0.5 mm

One gm of marketed product of nimesulide was separately applied on goat ear skin. The temperature of diffusion cell was maintained at 32 ± 0.5^{0}C. The air bubbles formed bellow the membrane was removed by tilting the cell till the removal of air bubbles through the sampling arm. All the diffusion cells were covered with aluminum foil to avoid contamination/ evaporation of permeation media. A 3-3 ml aliquot of drug permeation fluid was withdrawn at different time intervals. After sampling, same volume of fresh medium was replaced into the diffusion cell after each withdrawal. The withdrawn samples were analyzed on UV visible spectrophotometer (Shimadzu, 1700) at 391 nm. The cumulative amount of drug permeated across the goat ear skin was calculated. The in-vitro permeation of marketed product of nimesulide was reported in Fig. 10 and comparative data of drug permeation from marketed topical gel and developed aqueous topical gel formulation (formulation code Nimesu-K-G) is compiled in table 11

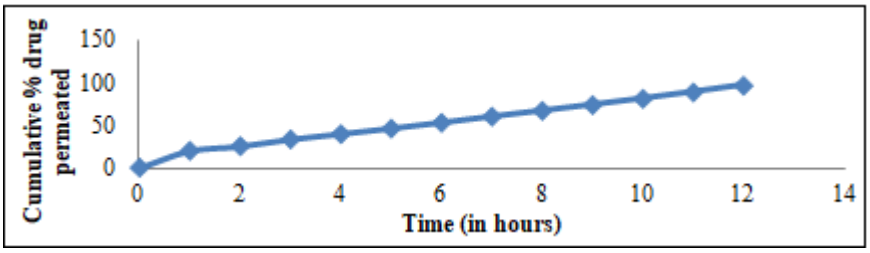

Figure 9: Cumulative amount of drug permeated through goat ear skin from aqueous topical gel formulation

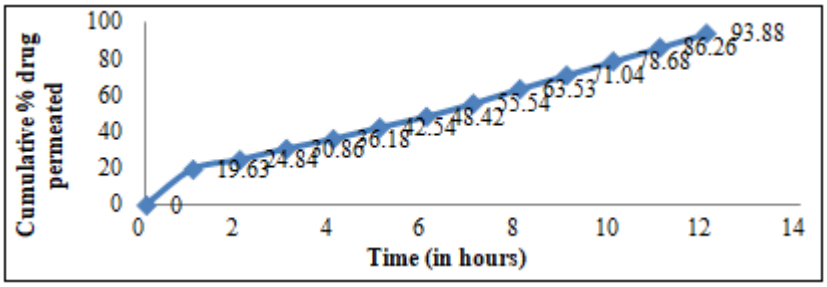

Figure 10: Cumulative amount of drug permeated through goat ear skin from marketed topical gel formulation

Table 11: Cumulative % drug permeated from formulated batch of topical gel and marketed formulation

S.No.	Formulation Code	Cumulative % drug permeated after 12 hr. studies
1.	Nimesu-K-G	97.47
2.	Marketed Gel	93.88

4. Conclusion

The concept of mixed solvency was successfully employed in formulating the topical solutions and gels of poorly water soluble drug, nimesulide. In this study, there was no involvement of organic solvent to prepare topical solution. The present study illustrates the novel application of mixed solvency concept to improve the drug solubility and permeability of nimesulide. Pharmaceutical companies may be benefited by this concept, not only to manufacture topical solution but also to develop other pharmaceutical formulations.

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